Improving data sets with regard to the biology and neurotrophic potential of enteroviruses other than polio

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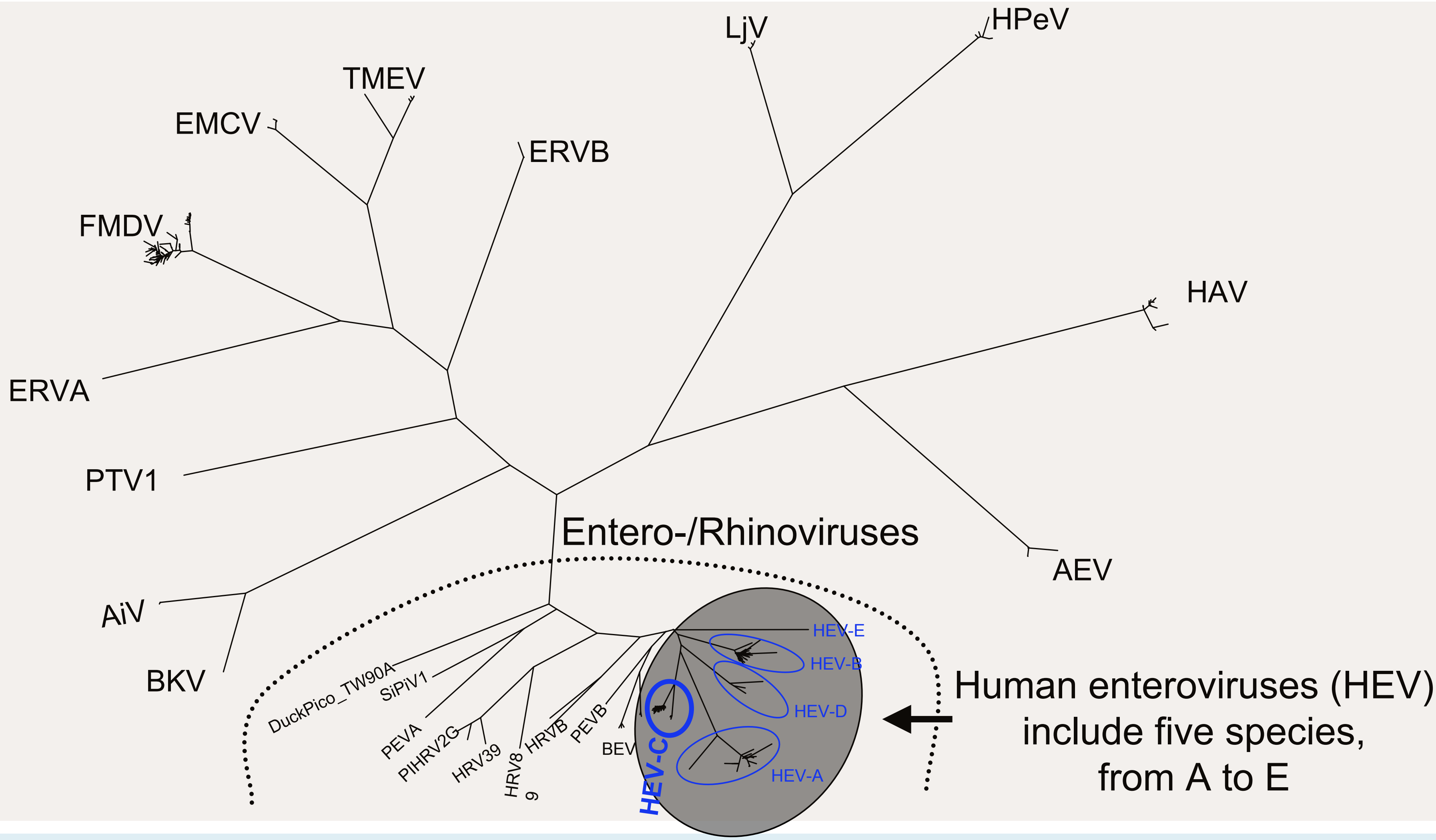
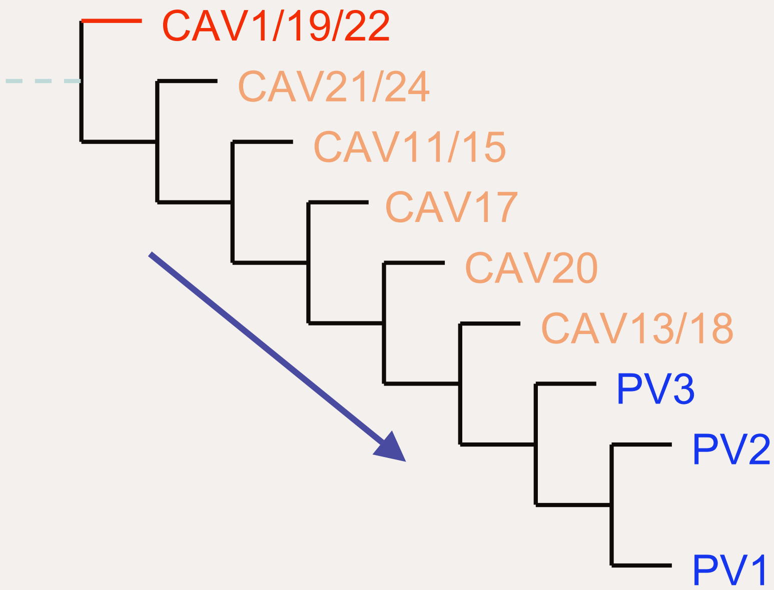
Picornaviridae: evolutionary tree

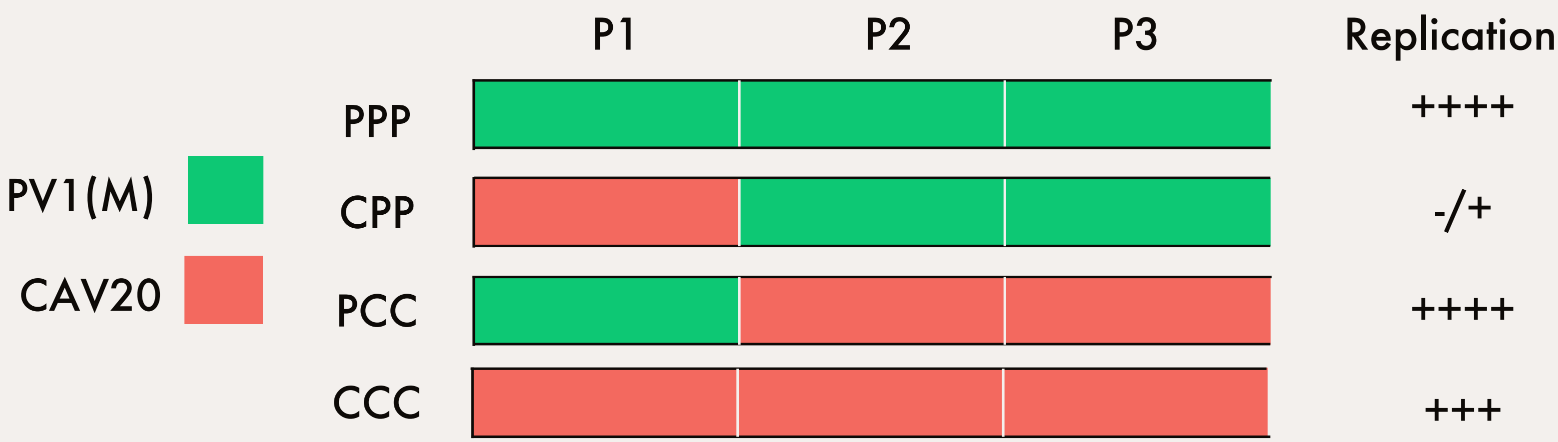


RdRp-based

HEV-C closely related viruses



Gorbalenya et al.



Jiang et al., ***2007***, *PNAS, 104: 9457-9462*

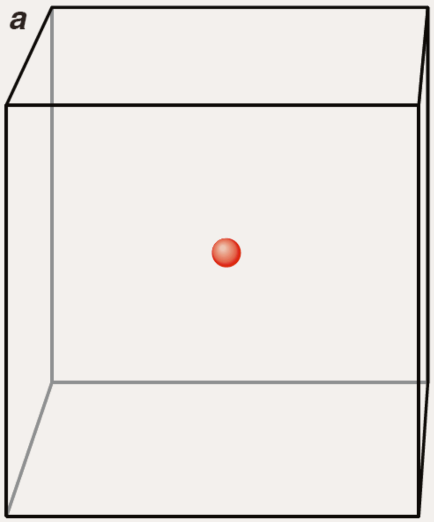
Implications for poliovirus eradication campaign

- PV evolved from a C-CAV ancestor
- Newly evolved CD155 specificity is favored over the ancestral ICAM specificity
- Homologous recombination or genetic drifting?

Global poliovirus eradication campaign assumes that PV has no natural reservoir but humans

A 'natural silent reservoir' may be present INSIDE human population: widespread, diverse and closely related C-CAVs

The "imperfect" replication



PERFECT REPLICATION
OF WILD TYPE

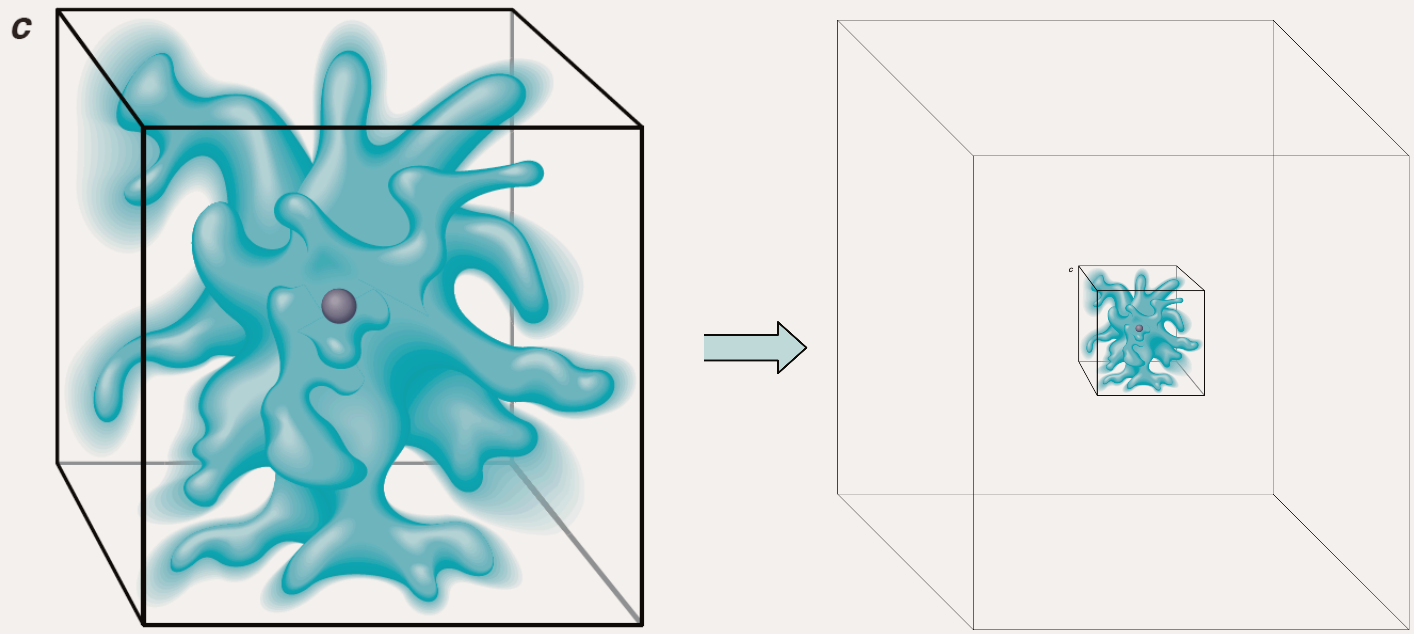
(Eigen, M. *et al.*, 1993)

Quasispecies

- The virus population is a collection of interdependent mutants
- The structure of the quasispecies is determine by:

    1) error rate of the RdRp
    2) recombination rate between different genomes
    3) selective pressures

Lessons from a high fidelity poliovirus mutant

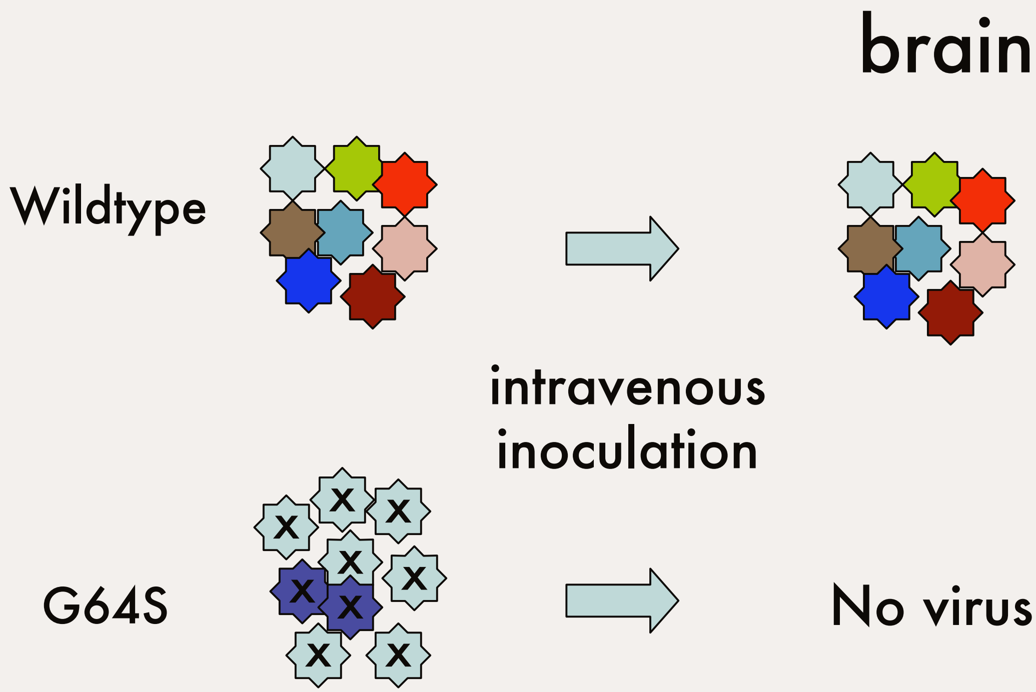


Wildtype (2.0 mut/gen)
- Pathogenic
- Transmissible

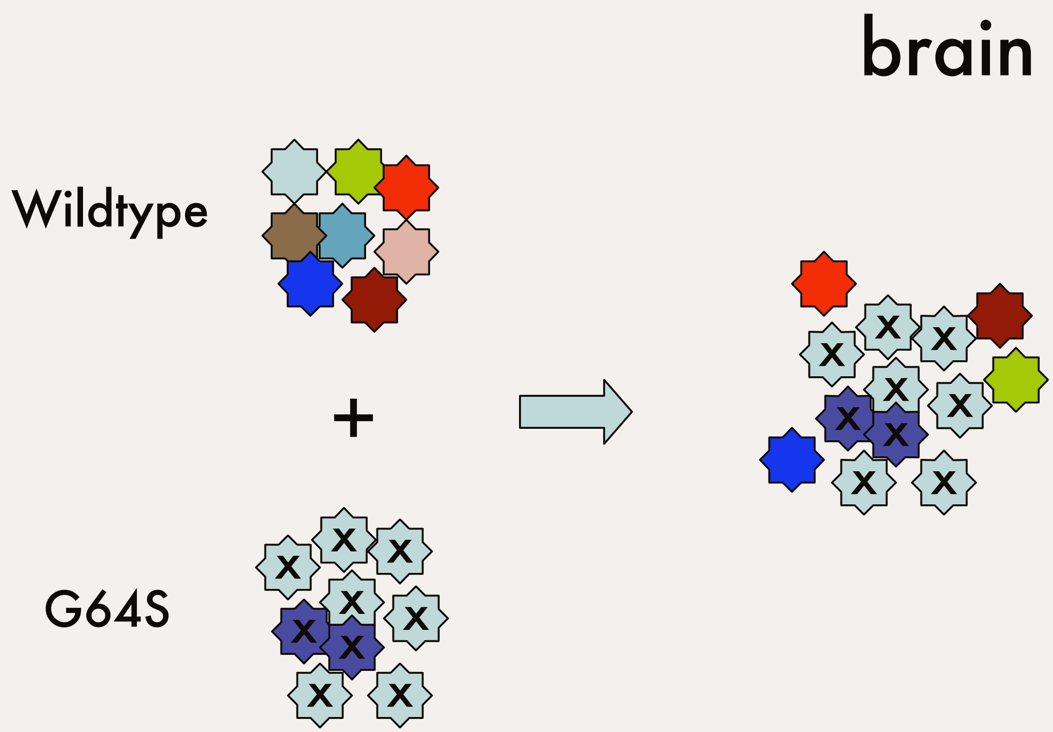
G64S (0.3 mut/gen)
- Non-pathogenic
- Not shedding

(Kirkegaard, Cameron, Andino *et al.*)

Cooperativity between members of the quasispecies



Cooperativity between members of the quasispecies



(Vignuzzi et al. Nature, 2006)

Mutual aid : A factor of evolution

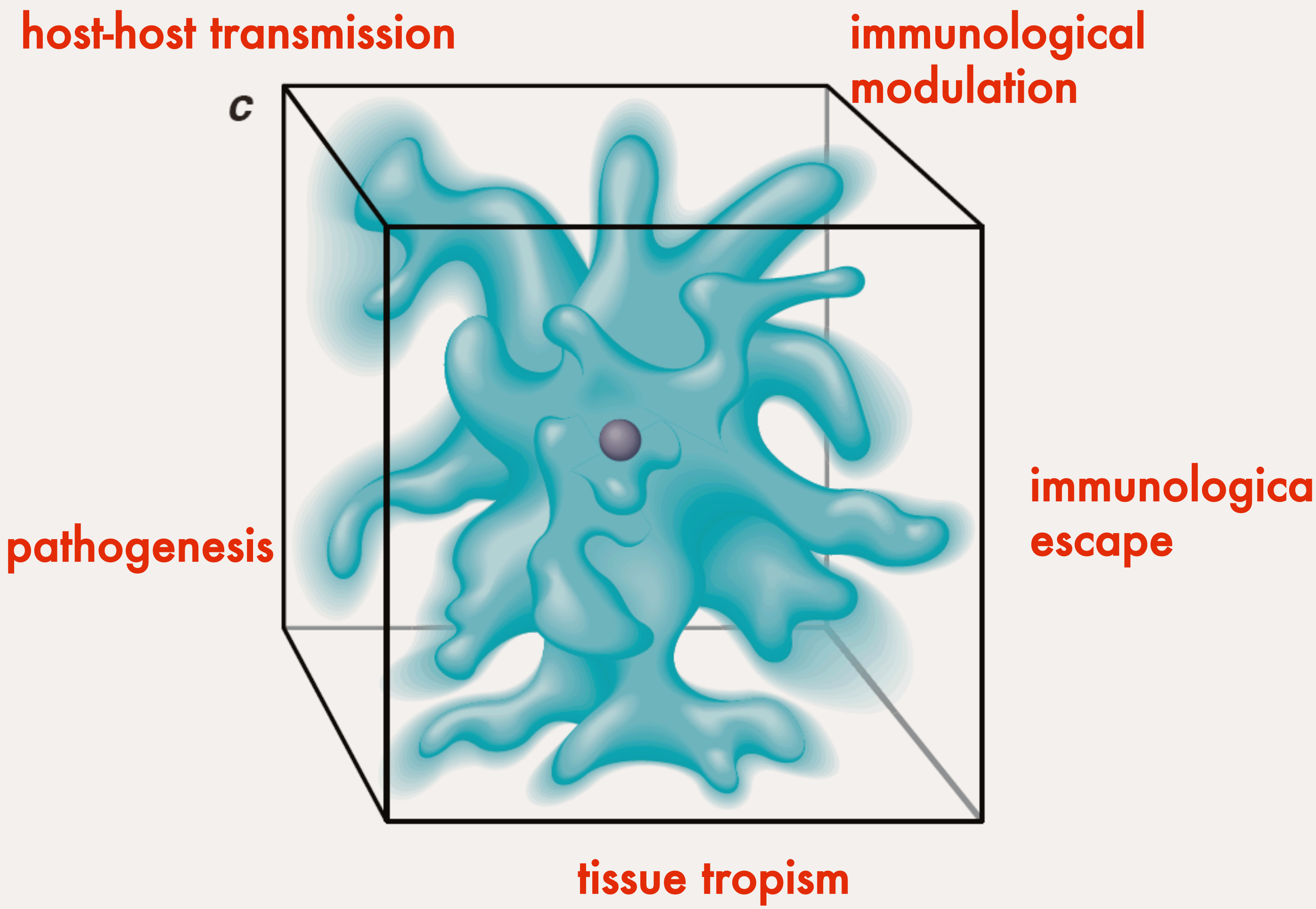
Peter Kropotkin

Survival of the Fittest

Individual or Population?

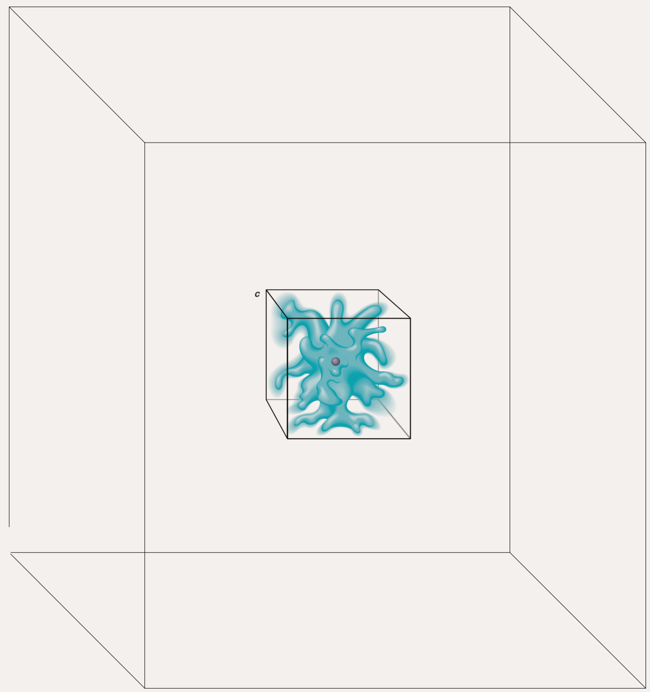
“cooperation and mutual aid are as important to evolution as competition and mutual strife”

Specialized subpopulations



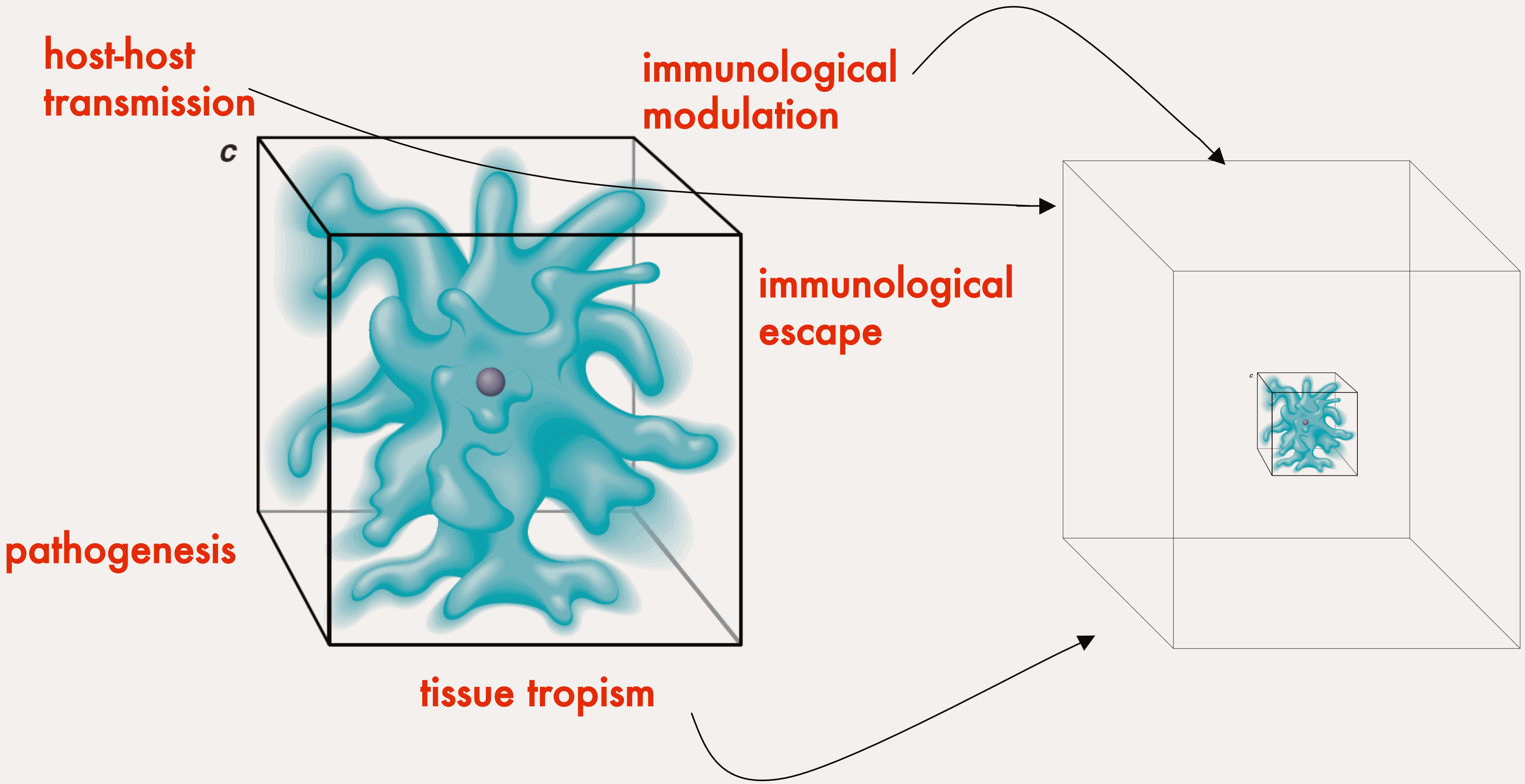
Reduced diversity = reduced functionality

replication



immunological
escape

Cooperative interactions



Conclusions

- The evolvability of a given virus population depends on the structure of the quasispecies
- Error rates and recombination shape up the population genetic structure
- Positive and negative interaction among members of the population determines the ability of the virus population to successfully navigate the environment

a) New methods to explore the quasispecies structure

- Consensus sequences contains little information
- **Error rates**, in vivo
- **Error frequency** (what is the degree of definition required?)
- **Sequence space** of the population (spatial representation vs time-scale representation)
- **Dynamic** nature of the quasispecies (traditional sequencing approaches inadequate)
- **Particle/PFU ratios**: coinfection rates

b) Defining the effect of the interactions between viruses

- Positive and negative effects on **pathogenesis** and **transmissibility**
- Exploring interactions between **different viruses/pathogens**, including other enteroviruses
- What are the **mechanisms** underlying these interaction?
  -recombination vs complementation
  -cellular vs systemic complementation
  -defining the functions of different subpopulation

c) Small animal models

- Define correlation between **transmissibility** and **pathogenesis** with the structure of the quasispecies
- Explore the dynamic nature of the evolution of the virus in **complex environments** (in vivo)
- Examining how **human interventions** (vaccines and drugs) may alter the pathways of evolution

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